

REMARKS

After entry of the amendment claims 1, 22 and 26-32 are pending.

Claims 1 and 22 have been amended to include the amounts of N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate and hydralazine hydrochloride administered and are supported by claims 5, 24 and 25 and the specification at, for example, page 50, lines 12 to 20 and page 51, lines 10 to 13. In view thereof, claims 5, 21, and 23-25 have been cancelled.

Claims 26-32 are supported by the specification at, for example, page 2, lines 17 to 19; page 2, line 30 to page 3, line 2; page 41, lines 1 to 2 and lines 19 to 21; page 42, lines 8 to 10 and 28 to 30; page 50, line 20 to page 51, line 9.

No issues of new matter should arise and entry of the amendment is respectfully requested.

I. Rejection under 35 U.S.C. §103

Claims 1, 5, and 21-25 are rejected under 35 U.S.C. §103(a) as being unpatentable over Stamler et al (US 6,472,390) in view of Adams et al (US 6,747,063) and over Goodman (US 6,087,398) in view of Loscalzo (US 6,635,273).

Applicants respectfully traverse the rejection and respectfully submit that the claimed invention is unobvious over the cited references.

Pending claims 1 and 26-32 are directed to the treatment of sickle cell anemia or thalassemia comprising administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate and hydralazine hydrochloride, wherein the N-hydroxy-L-arginine is administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day; and the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 300 milligrams per day.

Stamler is cited by the Examiner for the treatment of sickle cell anemia by the administration of a NO donor. Stamler does not even mention N-hydroxy-L-arginine, isosorbide dinitrate or

isosorbide mononitrate in the examples of NO donors that could be used for the treatment of sickle cell anemia. At column 4, lines 33 to 48, Stamler states:

“Examples of S-nitroso compounds including S-nitrosothiols useful herein include, for example, S-nitrosoglutathione, S-nitroso-N-acetylpenicillamine, S-nitroso-cysteine and ethyl ester thereof S-nitroso cysteinyl glycine, S-nitroso-gamma-methyl-L-homocysteine, S-nitroso-L-homocysteine, S-nitroso-gamma-thio-L-leucine, S-nitroso-delta-thio-L-leucine, and S-nitrosoalbumin. Examples of other NO donors useful herein are sodium nitroprusside (nipride), ethyl nitrite, nitroglycerin, SIN1 which is molsidomine, furoxamines, N-hydroxy (N-nitrosamine) and perfluorocarbons that have been saturated with NO or a hydrophobic NO donor.”

Additionally Stamler does not provide any guidance as to the amounts of a NO donor that would be necessary to treat sickle cell anemia. At column 5, lines 50 to 62, Stamler states (emphasis added):

“In general, administering a therapeutically effective amount for the first embodiment involves administration in an amount to achieve a concentration of NO donor in the blood of 100 picomolar to 100 micromolar (**depending on the drug administered and the disease treated or at risk for**) which is less than the amount which acutely lowers mean arterial blood pressure more than 10%, e.g., by more than 5%, for example, less than amounts causing at least 50% smooth muscle relaxation, ie., micromolar amounts, or to achieve concentration less than that which lowers pulmonary artery pressure more than 10%, e.g., by more

than 5%. Amounts of drug will vary depending on NO donor as well as disease state.”

Hence there is no teaching, suggestion or motivation by Stamler to treat sickle cell anemia by administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate, wherein the N-hydroxy-L-arginine is administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; and the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day.

Adams is cited by the Examiner in teaching that N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate are NO donors. Adams is directed to the use of a low dose of a NO donor for decreasing the pain associated with use of a prostaglandin for the treatment of erectile dysfunction wherein the NO donor is used at a unit dose of about **0.88 μmole or less** (see claim 1). The present invention is directed to the administration of N-hydroxy-L-arginine in an amount of about 1 grams to about 30 grams (i.e. 5 mmoles to about 157 mmoles); isosorbide dinitrate in an amount of about 20 milligrams per day to about 200 milligrams per day (i.e. 84.7 μmoles to about 847 μmoles per day); and isosorbide mononitrate in an amount of about 15 milligrams per day to about 200 milligrams per day (i.e. 78.5 μmoles to about 1.047 mmoles per day). Hence there is no teaching, suggestion or motivation by Adams to treat sickle cell anemia by administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate, wherein the N-hydroxy-L-arginine is administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day. In fact Adams teaches away from administering the high amounts of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate recited in the present invention.

As pointed out by the Examiner, neither Stamler nor Adams mention of the use of a hydralazine compound (i.e. antioxidant) either alone or in combination with a nitric oxide donor for the treatment of sickle cell anemia. Additionally as discussed above there is no suggestion or

motivation by Stamler or Adams to treat sickle cell anemia by administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate in combination with a hydralazine hydrochloride, wherein the N-hydroxy-L-arginine is administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day and the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 300 milligrams per day.

Goodman is cited by the Examiner for teaching methods of treating sickle cell anemia by administering an antioxidant. Goodman is directed to the treatment of sickle cell anemia by the administration of an acceptable dose of a reducing agent such as n-acetyl cysteine at **70 mg/kg to about 140 mg/kg** i.e. 6.3 g per day to about 13.5 g per day (see, column 9, lines 3 to 6). As discussed previously hydralazine compounds are structurally very different from N-acetyl cysteine, dithiothreitol, cysteamine, dimercaprol and succimer disclosed by Goodman (see, column 8, lines 64-65 and claim 2). In the present invention hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 300 milligrams per day. Goodman does not disclose or suggest of the use of a NO donor (i.e. N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate) either alone or in combination with a hydralazine hydrochloride (i.e. antioxidant) for the treatment of sickle cell anemia. Hence based on the teachings in Goodman, there is no motivation for one skilled in the art to treat sickle cell anemia by administering hydralazine hydrochloride in combination N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate, wherein the N-hydroxy-L-arginine is administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day and the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 300 milligrams per day.

Goodman does not cure the deficiencies of Stamler and Adams. Goodman does not provide any teaching, motivation or suggestion to modify Stamler and Adams to arrive at the claimed

invention to treat sickle cell anemia by administering hydralazine hydrochloride in combination N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate, wherein the N-hydroxy-L-arginine is administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day and the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 300 milligrams per day. In view thereof, Stamler and Adams in combination with Goodman do not motivate one to arrive at the present invention.

Loscalzo is cited by the Examiner for teaching that hydralazine and hydralazine compounds are known antioxidants. Applicants respectfully submit that Loscalzo does not disclose the treatment of sickle cell anemia by the administration of a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate in combination with hydralazine hydrochloride. Additionally the vascular diseases disclosed by Loscalzo are very different from sickle cell anemia of the present invention. Moreover there is no suggestion or motivation by Loscalzo to treat sickle cell anemia by administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate in combination with hydralazine hydrochloride, wherein the N-hydroxy-L-arginine is administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day and the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 300 milligrams per day.

Loscalzo does not cure the deficiencies of Stamler, Adams and Goodman. Loscalzo does not provide any teaching, motivation or suggestion to modify Stamler, Adams and Goodman to arrive at the claimed invention. In view thereof, Stamler and Adams in combination with Goodman and Loscalzo do not motivate one to arrive at the present invention.

Pending claims 22 and 26-32 are directed to the treatment of thalassemia comprising administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate and hydralazine hydrochloride, wherein the N-hydroxy-L-arginine is

administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day; and the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 300 milligrams per day.

As mentioned above, the discussion of which is incorporated herein in its entirety, Stamler, Adams and Goodman in view of Loscalzo do not disclose methods for the treatment of thalassemia comprising administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate and hydralazine hydrochloride, wherein the N-hydroxy-L-arginine is administered in an amount of about 1 grams to about 30 grams; the isosorbide dinitrate is administered in an amount of about 20 milligrams per day to about 200 milligrams per day; the isosorbide mononitrate is administered in an amount of about 15 milligrams per day to about 200 milligrams per day; and the hydralazine hydrochloride is administered in an amount of about 30 milligrams per day to about 300 milligrams per day.

In view of the above, Applicants respectfully submit that the claims of the present invention are unobvious over the cited references, alone and in combination, and respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

II. Conclusion

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 08-0219, under Order No. 0102258.00375US2 from which the undersigned is authorized to draw.

Respectfully submitted,

Dated: April 5, 2010

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